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Dec. 30, 2005 by Kay Bulen Kay Bulen  
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### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Laird et al.  
Application No.: 10/016,505  
Filed: December 10, 2001  
For: PROCESS FOR HIGH THROUGHPUT DNA METHYLATION ANALYSIS  
Art Unit: 1634  
Examiner: Jeanine Anne Goldberg  
Docket No.: 47675-62  
Date: December 30, 2005

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

### SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Sir:

Pursuant to the requirements in 37 C.F.R. § 1.56, and in conformance with 37 C.F.R. 1.97 and 1.98, Applicants hereby submit an Information Disclosure Statement. Applicants respectfully request that the Examiner: (1) consider the following documents during the course of his or her examination of the above-identified patent application, and (2) list the following documents in the References Cited section of any patent that may issue from the above-identified patent application.

Applicants cite 2 references listed on the attached form. The order of these references

should not be construed to suggest their relative pertinence. The Examiner is encouraged to review the entire disclosure of each reference in order to draw his or her own conclusions concerning the pertinence of the references to the claimed subject matter of this application. The filing of this Information Disclosure Statement should not be construed to suggest that a patentability search has been made or that the cited references are prior art or are considered to be material to patentability.

These documents came to the attention of the Applicants through a Communication from the European Patent Office in a related European patent application, which has now been allowed.

Applicants respectfully request consideration of the foregoing documents during examination of the above-identified patent application. Applicants have enclosed a completed Information Disclosure Statement by Applicant and copies of the two literature documents.

Applicants provide the following comments relative to these references:

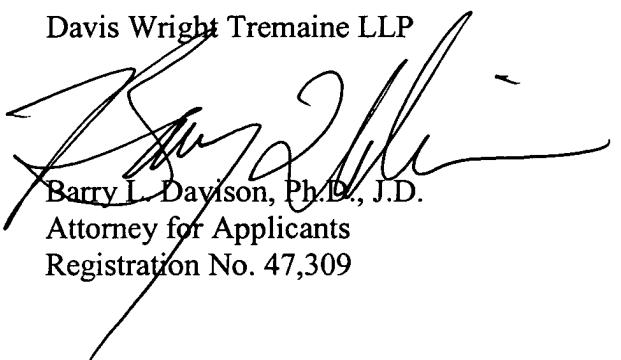
Reference O16 describes allelic discrimination at the level of a single base substitution using fluorogenic probes (*e.g.*, TaqMan probes) and the 5' nuclease assay with Taq polymerase (see, *e.g.*, Abstract). Significantly, however, O16 actually teaches the use of two different fluorescence indicator dyes (*e.g.*, FAM and TET; one for each allele-specific probe) along with end-point analysis and determination of a fluorescence spectrum. In O16 endpoint analysis and specific software is used to perform multicomponent analysis to determine the relative contributions of each dye to the observed fluorescence spectrum. For example, at page 144, first full paragraph, O16 teaches that "Genotyping with fluorogenic probes requires that fluorescence measurements be made after PCR in completed" (see also legend to Fig. 3, reciting "After PCR amplification, an endpoint fluorescence reading was made on the ABI PRISM 7700. As explained in the text, the fluorescence spectra were analyzed for generate a normalized Allele 1 value and a normalized Allele 2 value for each sample"). Therefore, O16 does not in fact teach real time allelic discrimination at the level of a single base substitution using fluorogenic probes (*e.g.*, TaqMan probes) and the 5' nuclease assay, and rather *teaches away* from the present invention by teaching that such allele discrimination cannot be achieved without the use of two different fluorescence indicator dyes (*e.g.*, FAM and TET) along with end-point analysis and determination of a fluorescence spectrum. Additionally, O16 teaches that virtually any/all effective applications of this technology to allelic discrimination require that such allele

discrimination cannot be achieved without the use of two different fluorescence indicator dyes (e.g., FAM and TET) along with end-point analysis and determination of a fluorescence spectrum. Therefore, O16 not only teaches away, but broadly and explicitly teaches away. Moreover, O16 does not teach quantification (as provided by preferred embodiments of the present invention), but rather teaches effective discrimination among four normalized groups/statuses. Furthermore, there is no teaching or suggestion in O16, or in any other of the previously or presently asserted references to combine this or any other such fluorescence based assay with methylation analysis, much less with methylation analysis using methylation specific probes on a real-time high-throughput basis, quantitative or otherwise.

O17 is merely another example of an isolated and limited application of real-time detection of single nucleotide polymorphism (in this instance in orthopoxviruses and the human C6 gene) using the 5' nuclease PCR technique, and specifically using a portable, battery-powered miniature analytical system. As for O16, there is no teaching or suggestion whatsoever in O17, alone or in combination with any other of the previously or presently asserted references to combine this or any other such fluorescence based assay with methylation analysis, and certainly not with methylation analysis using methylation specific probes on a real-time high-throughput basis, quantitative or otherwise.

Respectfully submitted,

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<b>Substitute for form 1449/PTO</b>  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (Use as many sheets as necessary)				<b>Complete if Known</b>	
				Application Number	10/016,505
				Filing Date	December 10, 2001
				First Named Inventor	Laird
				Art Unit	1634
				Examiner Name	Jeanine Anne Goldberg
Sheet	1	of	2	Attorney Docket Number	47675-62

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code <sup>2</sup> (if known)			
		US-			

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T <sup>6</sup>
		Country Code <sup>3</sup> -Number <sup>4</sup> -Kind Code <sup>5</sup> (if known)				

Examiner Signature		Date Considered	
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\*EXAMINER: Initial if reference considered, whether or not citation is in conformation with MPEP 609. Draw line through citation if not in conformation and not considered. Include copy of this form with next communication to applicant. <sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04 <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard St. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

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				Application Number	10/016,505
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				First Named Inventor	Laird
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				Examiner Name	Jeanine Anne Goldberg
Sheet	2	of	2	Attorney Docket Number	47675-62

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
	O16	LIVAK, Allelic discrimination using fluorogenic probes and the 5' nuclease assay, Genetic Analysis: Biomolecular Engineering 14:143-149, 1999	
	O17	IBRAHIM et al., Real-Time Microchip PCR for Detecting Single-Base Differences in Viral and Human DNA, Anal. Chem. 70:2013-2017, 1998	

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